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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/903,063	07/11/2001	Jack R. Wands	21486-032DIV3	1087

30623 7590 02/28/2003

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EXAMINER
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ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 02/28/2003

14

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/903,063	Applicant(s) Wands et al
	Examiner Karen Canella	Art Unit 1642

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3 months* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☐ Responsive to communication(s) filed on _____.

2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under ***Ex parte Quayle***, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *23-25 and 39-53* is/are pending in the application.

4a) Of the above, claim(s) *45, 47, 52, and 53* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *23-25, 39-44, 46, and 48-51* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 7
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Acknowledgment is made of applicant's election of species 1, liver cancer. Claims 23-25 and 39-53 are pending. Claims 45, 47, 52 and 53, drawn to non-elected species, are withdrawn from consideration. It is noted that applicant indicated that claim 47, drawn to cholagiocarcinoma read on the elected species. However, cholangiocarcinoma is a cancer of the bile ducts, which corresponds to a separate species as set forth in Paper No. 10. Claims 23-25, 39-44,46, and 48-51 are examined on the merits.

Oath/Declaration

2. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

Non-initialed and/or non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c).

Specification

3. The disclosure is objected to because of the following informalities:

(A) The specification is objected to as not complying with 1.821(d) of the Sequence Rules and Regulations. The specification contains numerous recitations of HAAH. One species of HAAH is identified in Table 1 as SEQ ID NO:2, encoded by SEQ ID NO:3 (Table 2). The specification refers to other species of HAAH encoded by cDNAs in Table 4 (page 47). When the specification of a patent application discusses a sequence listing that is set forth in the "Sequence Listing" in accordance with paragraph (c) of the Sequence Rules and Regulations, reference must be made to the sequence by use of the assigned identifier, in the text of the description or claims of the patent application. Without a sequence identifier, it is unclear if a

reference to HAAH in the specification is synonymous with SEQ ID NO:2. Appropriate correction is required.

(B) Page 6, line 16 contains a blank space after "SEQ ID NO".

Appropriate correction is required.

Claim Objections

4. Claims are objected to as not complying with 1.821(d) of the Sequence Rules and Regulations. Claims 26 recites HAAH. Claim 27 recites "EGF-like repeat sequence". Table 1 identified HAAH as SEQ ID NO:2. The specification identifies SEQ ID NO:4 as the EGF-like repeat sequence. When the claims of a patent application discusses a sequence listing that is set forth in the "Sequence Listing" in accordance with paragraph (c) of the Sequence Rules and Regulations, reference must be made to the sequence by use of the assigned identifier, in the text of the description or claims of the patent application. Appropriate correction is required.

5. Claim 42 is objected to because of the following informalities: the typographical error of "and IRS phosphorylation site" rather than --an IRS phosphorylation site---. Appropriate correction is required.

Claim Rejections - 35 USC § 112

6.The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 23-25, 39-44, 46 and 48-51 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are rended vague and indefinite by recitation of "IRS" in claims 23, 24 and 29 and the recitation of "HAAH" in claim 25 are indefinite in the recitation of "IRS" as the only means of identifying the proteins upon which the claimed methods are based. The use of

laboratory designations only to identify a particular protein renders the claims indefinite because different laboratories may use the same laboratory designations to define completely distinct proteins. Amendment of the claims to incorporate a sequence identifier would overcome this rejection.

Claim 40 is vague and indefinite by reference to an object which is variable. EB1089 is a trade name; the compound represented by EB1089 can be altered with time.

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 23-25, 39-44, 46, 48-51 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inhibiting tumor growth in a mammal comprising the administration of a drug which is internalized by said tumor cell wherein said drug inhibits or blocks the tyrosine phosphorylation of IRS-1, or a method of inhibiting tumor growth in a mammal comprising the expression of dominant-negative mutants of IRS-1 wherein said dominant negative mutants inhibit the phosphorylation of tyrosines on IRS-1, does not reasonably provide enablement for a method of inhibiting tumor growth comprising the administration of a compound which inhibits signal transduction through the IRS pathway by means other than inhibiting the phosphorylation of IRS-1, or a method of inhibiting tumor growth in a mammal comprising the administration of an antibody or a protein which binds to the residues of IRS-1 which are phosphorylated in response to activation of the insulin receptor. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to the invention commensurate in scope with these claims.

The first paragraph of 35 U.S.C. 112 states that "the specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full,

clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same...". The courts have interpreted this to mean that the specification must enable one skilled in the art to make and use the invention without undue experimentation. The courts have further interpreted undue experimentation as requiring "ingenuity beyond that to be expected of one of ordinary skill in the art" (Fields v. Conover, 170 USPQ 276 (CCPA 1971)) or requiring an extended period of experimentation in the absence of sufficient direction or guidance (In re Colianni, 195 USPQ (CCPA 1977)). Additionally the courts have determined that "...where a statement is , on its face, contrary to generally accepted scientific principles", a rejection for failure to teach how to make/or use is proper (In re Marzocchi, 169 USPQ 367 (CCPA 1971)). Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph have been described in In re Colianni, 195 USPQ 150, 153 (CCPA 1977) and have been clarified by the Board of Patent Appeals and Interferences in Ex parte Forman, 230 USPQ 546 (BPAI 1986). Among the factor are the nature of the invention, the state of the prior art, the predictability or lack thereof in the art, the amount of direction or guidance present, the presence or absence of working examples, the breadth of the claims, and the quantity of experimentation needed. The instant disclosure fails to meet the enablement requirement for the following reasons:

The specification sets forth mutants of the IRS-1 protein which could be used to define the link between the IRS signal transduction pathway and the activation of HAAH as a downstream effector gene. The specification contemplates mutations in the C-terminus of the IRS-1 molecule which would abolish the domains which bind to SH2 effector proteins such as Grb2, Syp, and PI3K. The specification specifically notes the construction of the double mutant wherein phenylalanine replaced tyrosine at positions 897 and 1180 of IRS-1. The results of the transfection of said mutants on the expression of the HAAH gene were not disclosed. The specification also states that "Antibodies or other compounds which bind to phosphorylation sites or inhibit phosphorylation at hose sites are used to inhibit signal transduction and thus

proliferation of HAA-overexpressing tumors", but no disclosure of specific antibodies, or means for said antibodies to be internalized within tumor cells are taught by the specification.

The prior art teaches that vitamin B analogues and wortmannin are taken up by cells and result in the inhibition of phosphorylation of IRS-1 and the loss or reduction of signaling through the IRS-1 pathway. The art teaches that the IRS-1 protein is located within the cytoplasm of the cell, and tyrosine phosphorylation upon activation of the insulin receptor by insulin or an antagonist thereof can result in the transmission of an activation signal to . The art teaches that the phosphorylated IRS-1 can transmit an activation signal to downstream molecules containing the Src homology domain and through activation of PI3 kinase (for instance see White, Molecular and Cellular Biochemistry, 1998, vol.182, pp. 3-11, figure 1 and Ogawa et al Molecular and Cellular Biochemistry, 1998, vol. 182, pp. 13-22, figure 5). However, the art also teaches that serine phosphorylation of IRS-1 contributes to the activation of IRS-1 as well (Li et al, The Journal of biological chemistry, 1999, Vol. 274, pp. 9351-9356), and it has been shown that treatment of cells with PDGF inhibits the IRS signaling pathway via the akt pathway, and endothelin-1 inhibits the IRS pathway via the MAP kinase pathway and the serine phosphorylation of IRS-1. Thus, the IRS signaling pathway is affected by numerous proteins and phosphorylation of serine residues as well as tyrosine residues.:

The instant claims are broadly drawn to a method of inhibiting tumor growth by means of inhibiting signal transduction through the IRS signal transduction pathway, and thus include all pathways which include IRS-1, and the activation of IRS-1 through any means beyond phosphorylation of tyrosine residues. Because signaling through IRS-1 is complex and encompassing pathways beyond the activation of Syc homology domains by tyrosine phosphorylation of IRS-1, it would require undue experimentation to practice the invention to the full scope of the claims. Further, it would also be undue experimentation to find an antibody or protein which would be taken up by a tumor cell and block the binding of the phosphorylation of IRS-1 without being bound to another protein in the internal milieu of the cell. It si well known in

the art that antibodies cannot penetrate the cytoplasm without being bound to a internalizing receptor. Further, it is well known in the art that antibodies must be tested for their affinity for a specific substrate within the context of the environment of said substrate in order to identify an antibody which would specifically bind to the desired substrate, and that many antibodies cross-react with other proteins than those to which they were raised. Given the lack of teachings of a single antibody which would fulfill the criteria of being taken up by the tumor cell and then internalized where said antibody would specifically bind to the phosphorylation domain of IRS-1, one of skill in the art would be subject to undue experimentation in order to carry out the invention a broadly claimed.

10. Claim 25 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claim 25 is drawn to a method of inhibiting tumor growth in a mammal comprising administering to said mammal a compound which inhibits the binding of Fos or Jun to an HAAH promoter sequence. The specification sets forth in Table 2, the cDNA for HAAH. The specification provides no written description of the polynucleotide sequence of the HAAH promoter sequence and therefore the written description is not commensurate in scope with the claims drawn to an HAAH promoter sequence.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the "written description" inquiry, whatever is now claimed. (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116).

Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (see page 115).

The nature of gene promoters is that they are variant sequences, unrelated in sequence to the polynucleotide which is expressed. The skilled artisan cannot envision the detailed structure of the encompassed polynucleotides and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of identification and isolation. Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Lts., 18 USPQ2d 1016.

Furthermore, In The Regents of the University of California v. Eli Lilly (43 USPQ2d 1398-1412) section B(1), the court held that "An adequate written description of a DNA...requires a precise definition, such as by structure, formula, chemical name, or physical properties, not a mere wish or plan for obtaining the claimed chemical invention". However, no disclosure beyond the mere mention of the HAAH promoter is made in the specification. This is insufficient to support the claim as provided by the Interim Written Description Guidelines published in the January 5, 2001 Federal Register at Volume 66, Number 4, pages 1099-1111.

Claim Rejections - 35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Claims 23, 24, 42, 44, 46 and 49 are rejected under 35 U.S.C. 102(b) as being anticipated by Tanaka et al (WO 98/19691). Claim 23 is drawn to a method of inhibiting tumor growth in a mammal comprising the administration of a compound which inhibits signal transduction through the IRS signal transduction pathway. Claim 24 embodies the method of claim 23 wherein said compound inhibits IRS phosphorylation. Claim 42 embodies the method of claim 23 wherein the IRS phosphorylation site is a phosphorylation site of SEQ ID NO:5. Claim 44 is drawn to the method of claim 2 wherein the tumor is liver cancer. Claim 46 specifies that the liver cancer is hepatocellular carcinoma. Claim 49 embodies the method of claim 23 wherein the compound is dominant negative IRS mutant. Tanaka et al disclose mutants of human IRS-1 that are dominant negative and inhibit signal transduction of the IRS pathway. Tanaka et al disclose a method of treating hepatocellular carcinoma comprising the administration of nucleic acid molecules encoding said mutants (page 1, lines 12-28 and page 6, lines 3-18). Tanaka et al do not specifically disclose that IRS-1 would comprise the amino acid sequence of SEQ ID NO:5, but the amino acid sequence would be inherent in human IRS-1 protein. Tanaka et al disclose that said mutant lack the tyrosine phosphorylation motifs of IRS-1 that are necessary for signaling to molecules containing the Src homology domain (page 2, lines 3-31). Thus, it is reasonable to conclude that the absence of tyrosine phosphorylation motifs in the mutant proteins results in inhibition of IRS-1 phosphorylation.

13. Claims 23, 24, 39, 40, 42 and 44 are rejected under 35 U.S.C. 102(a) as being anticipated by Morris (WO 98/56387) as evidenced by Rozen et al (International Journal of Oncology, 1999, Vol. 15, pp. 589-594). The embodiments of claims 23, 24, 42 and 44 are set forth above. Claim 39 embodies the method of claim 23 wherein said compound is a vitamin D analog. Claim 40 specifies that said analog is EB1089. Morris et al disclose a method for inhibiting liver cancer comprising the administration of vitamin D analogs such as EB1089 (page 5, line 29 to page 6, line 27). It is inherent in the method of Morris et al that the vitamin D analog inhibits signal transduction through the IRS signaling pathway.

Claim Rejections - 35 USC § 103

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

15. Claims 23, 24, 42, 44, 46, 49, 50 and 51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tanaka et al (WO 98/19691) in view of what is suggested by the reference. Claim 50 embodies the method of claim 49 wherein said mutant comprises a mutation at position 897 of SEQ ID NO:5. Claim 51 embodies the method of claim 49 wherein said mutant comprises a mutation at position 1180 of SEQ ID NO:5. Tanaka et al disclose position 897 as the IRS-binding site to Grb2 protein the 1180 position as the binding sit to the Syp phosphatase, both Grb2 and Syp being downstream effectors of the IRS-1 signaling pathway.

It would have been *prima facia* obvious to one of ordinary skill in the art at the time the claimed invention was made to mutate positions 897 and 1180 of IRS-1. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the

teachings of Tanaka et al on the specific binding sites for downstream effector molecules in IRS-1 signaling.

16. Claims 23, 24, 39, 40-42 and 44 rejected under 35 U.S.C. 103(a) as being unpatentable over Morris (WO 98/56387) in view of Ogawa et al (Molecular and Cellular Biochemistry, 1998, Vol. 182, pp. 13-22) and Rozen et al (International Journal of Oncology, 1999, Vol. 15, pp. 589-594). The embodiments of claims 23, 24, 39, 40, 42 and 44 are set forth above. Claim 41 embodies the method of claim 23 wherein said compound is wortmannin.

Morris et al teach a method for treating liver cancer comprising the administration of vitamin D analogs, specifically EB1089. Morris et al do not teach the administration of wortmannin.

Rozen et al teach that the vitamin D analog EB1089 inhibits the IRS-1 phosphorylation (abstract, lines 21-23).

Ogawa et al teach that wortmannin inhibits the downstream signaling from the IRS-1 molecule to the mTOR (page 18, figure 5).

Tanaka et al teach a method of treating liver cancer comprising the administration of dominant negative mutants of IRS-1 which lack tyrosine phosphorylation motifs.

It would have been *prima facia* obvious to one of ordinary skill in the art at the time the claimed invention was made to substitute wortmannin for EB1089 in the method of treating liver cancer as taught by Morris et al. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Rozen et al on the inhibition of IRS-1 phosphorylation by EB1089 and the teachings of Tanaka et al on the inhibition of tumor growth by dominant negative mutant which lack residues for phosphorylation and downstream signaling. One of skill in the art would conclude that wortmannin would inhibit downstream signaling of IRS-1 phosphorylation, and that said inhibition would be efficacious in the treatment

of liver cancer as EB1089 also inhibits the downstream signaling of the IRS-1 molecule by inhibiting phosphorylation of said molecule.

Conclusion

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Canella whose telephone number is (703) 308-8362. The examiner can normally be reached on Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Karen A. Canella, Ph.D.
Patent Examiner, Group 1642
February 24, 2003